rVSV-ZEBOV-GP Vaccine (V920): Development Update

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Partners and Collaborators

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Public Health Agency of Canada (PHAC)

NewLink Genetics (Bio-Protection Systems Corporation)

I Phase I Studies

WHO Clinical Consortium/ Wellcome Trust

wellcome trust

World Health Organization

- ✓ **Switzerland**: University Hospitals of Geneva
- ✓ **Germany:** University Medical Center Hamburg/Clinical Trial Center North
- ✓ **Gabon:** Centre de Recherches Medicales de Lambarene/University of Tuebingen
- ✓ **Kenya:** Kenya Medical Research Institute
- ✓ Marburg Laboratory

- CCV – Halifax, Canada
- US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA)
- NIAID/NIH
- BARDA

II/III Phase II/III Studies

- **Liberia:** Liberia – NIH Partnership (NIAID)

National Institutes of Health

- **Sierra Leone:** CDC/Sierra Leone Medical School

CDC Centers for Disease Control and Prevention

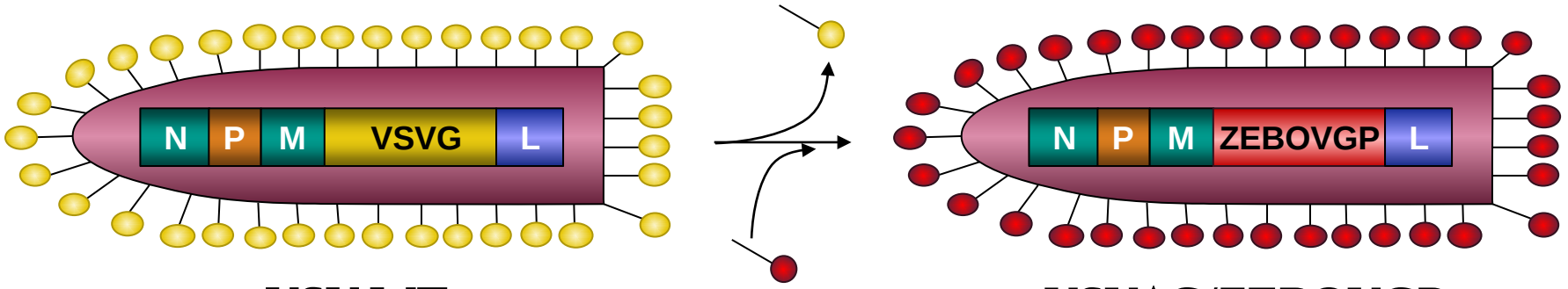
- **Guinea:** WHO/Norwegian Institute of Public Health//MSF/HealthCanada
- US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA), BARDA

Department of Defense

Note: Opinions, interpretations, conclusions, and recommendations in this presentation are those of the author and are not necessarily endorsed by the U.S. Army.

V920: rVSV-ZEBOV-GP Vaccine

- Vector = live attenuated recombinant vesicular stomatitis virus (rVSV)
  - Antigen = Zaire Ebola virus (ZEBOV) glycoprotein (GP)
  - VSV GP replaced with Ebola-Zaire GP
  - Replication competence facilitates use as a single-dose regimen



Cynomolgus macaque Ebola Viral Disease (EVD) model

- Intramuscular injection of confirmed wild-type genotype (7U) Ebola Kikwit proving uniformly lethal at target dose ranges of 10^4 to 10^{-2}* pfu (*estimated by dilution)
- Initial EVD signs (e.g. fever and/or viremia by RT-PCR) 3 to 6 days post IM exposure (100 to 1000 pfu target dose)
- Time to death ranges from 5 to 8 days post-exposure (100 to 1000 pfu target dose)
- Gross anatomic pathology consistent with EVD (enlarged, friable liver; skin rash; disseminated petechial hemorrhage; small intestinal hemorrhage)
- Microscopic lesions consistent with EVD infection

Slide courtesy of MCS-JVAP / USAMRIID

Key Assays Used in the Animal and Clinical Studies

- IgG ELISA
  - Method used in Phase I trials (USAMRIID)
  - Analogous method used for non-human primates
- Neutralizing antibody
  - Species neutral methods
  - Pseudovirion assay (PsVNA) used for most Phase I trials (USAMRIID)
  - Plaque-reduction (PRNT) assay intended to be applied for both human and NHP studies
- IgG ELISA and PRNT assays being validated
  - Validation planned (2H2015) to enable use for Phase III samples
- Other exploratory assays under development

Speaker Notes for Slide 5

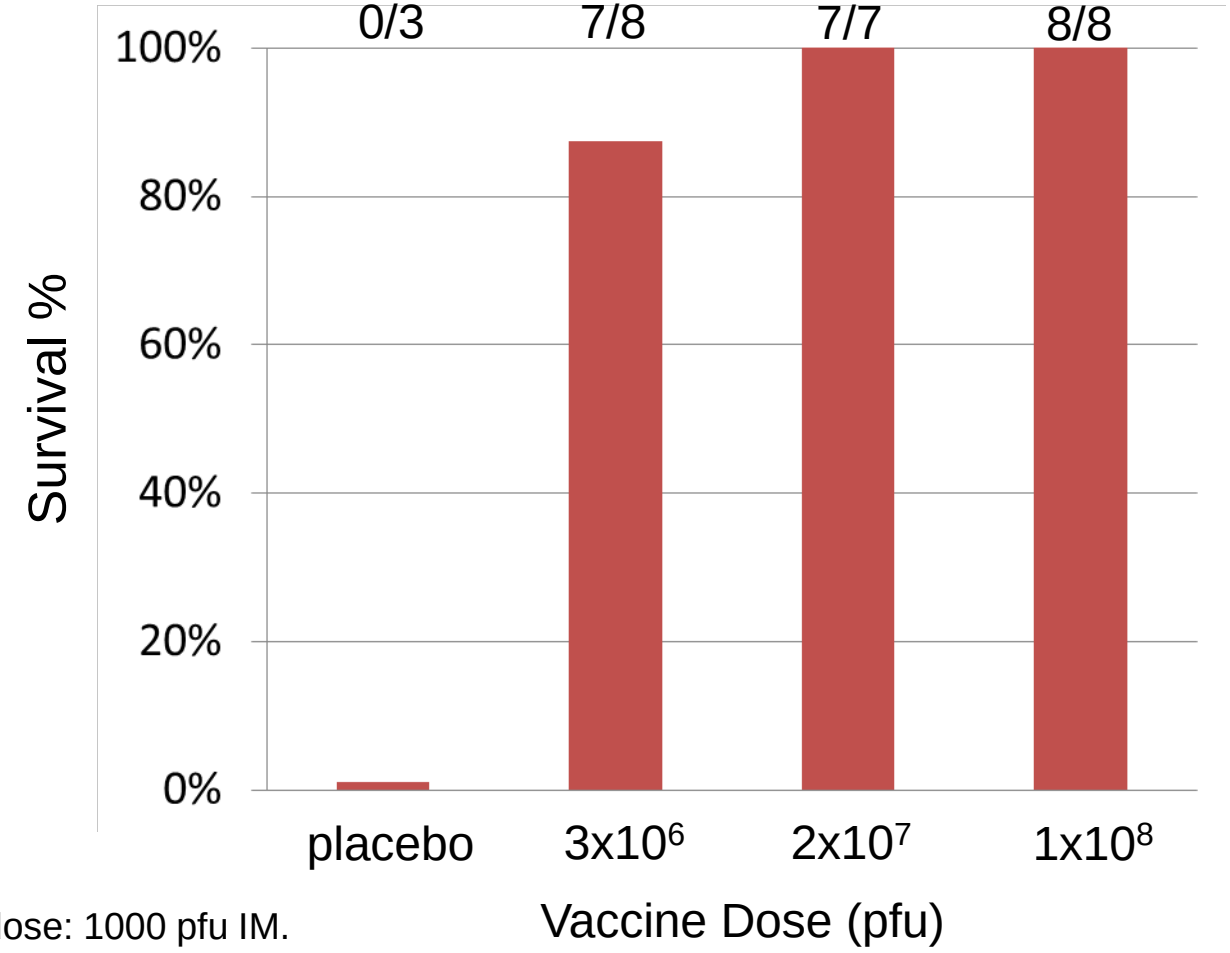
voice over IgG differences

rVSV-ZEBOV Vaccines Are Highly Protective in Challenge Models

- Protective in challenge models in multiple species, including mice, hamsters, guinea pigs and non-human primates (NHPs)[1-2]
- A single dose completely protects NHPs against high-dose (~1000 pfu) challenge[1,4-5]
- Protects NHPs even in relatively short periods before and shortly-after challenge
  - Complete protection against Makona (current epidemic strain) at Day -7, -14, -28 vs challenge; 67% protection at Day -3[6]
  - Partial protection (50%) when vaccinating 30 minutes *after* challenge[3]

1. Jones, et al. Nat Med (2005).
2. Wong, et al. Vaccine (2014).
3. Feldmann, et al. PLoS Pathog. (2007).
4. Geisbert, et al. Vaccine (2008)
5. Qiu, et al. PLoS One (2009)
6. Marzi, et al. *submitted* (2015)

V920 Protects Non-human Primates Against Lethal Ebola Challenge



Challenge dose: 1000 pfu IM.
Data provided by USAMRIID.
pfu=plaque-forming units.

rVSV-ZEBOV Vaccine-Induced Protection Appears to Be Primarily Antibody Mediated

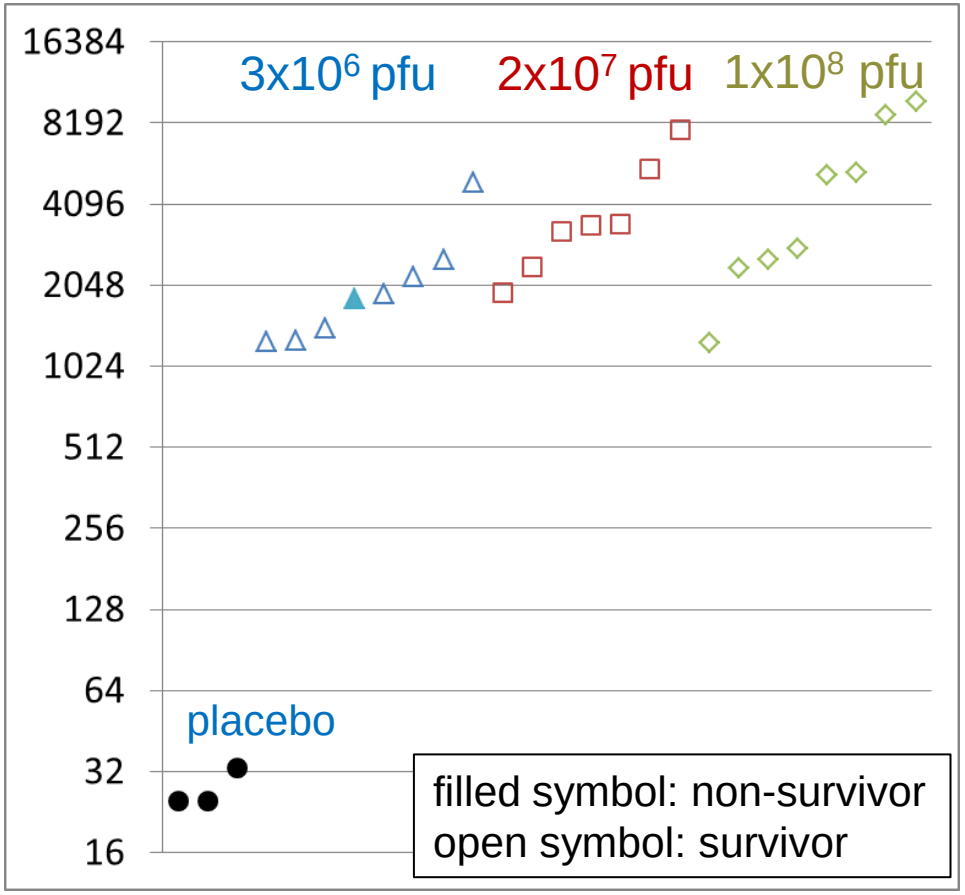
- IgG antibody levels correspond to survival in mouse and guinea pig challenges[1]
- Cell-mediated immunity does not appear critical to protection[2]
  - CD8+ T cell depletion of non-human primates at vaccination has no impact on survival
  - CD4+ T cell depletion at time of vaccination reduces survival, while depletion at time of challenge does not

1. Wong, et al. Vaccine (2014).
2. Marzi, et al. PNAS (2013).

V920 Is Immunogenic in Non-human Primates

Additional Data Needed to Establish a Threshold for Protection

Outcomes by IgG ELISA Titers (U/mL)



Unmeasurable titers assigned value of 25 for display.
Data provided by USAMRIID.
pfu=plaque-forming units.

- Additional challenge studies in planning to explore lower dose levels
- Overall intent is to establish a relationship between measures of immunity and survival

Speaker Notes for Slide 10

If have the neut data can speak to the two bullets

Clinical Program Status

- Eight Phase I studies in adults including over 550 vaccine recipients
  - Covered $3x10^3$ – $1x10^8$ pfu dose range
- Vaccine has been generally well tolerated
- $2x10^7$ pfu dose selected for Phase III studies
- Three Phase II/III efficacy/effectiveness studies ongoing

V920 Elicits a Robust and Rapid Antibody Response in Humans

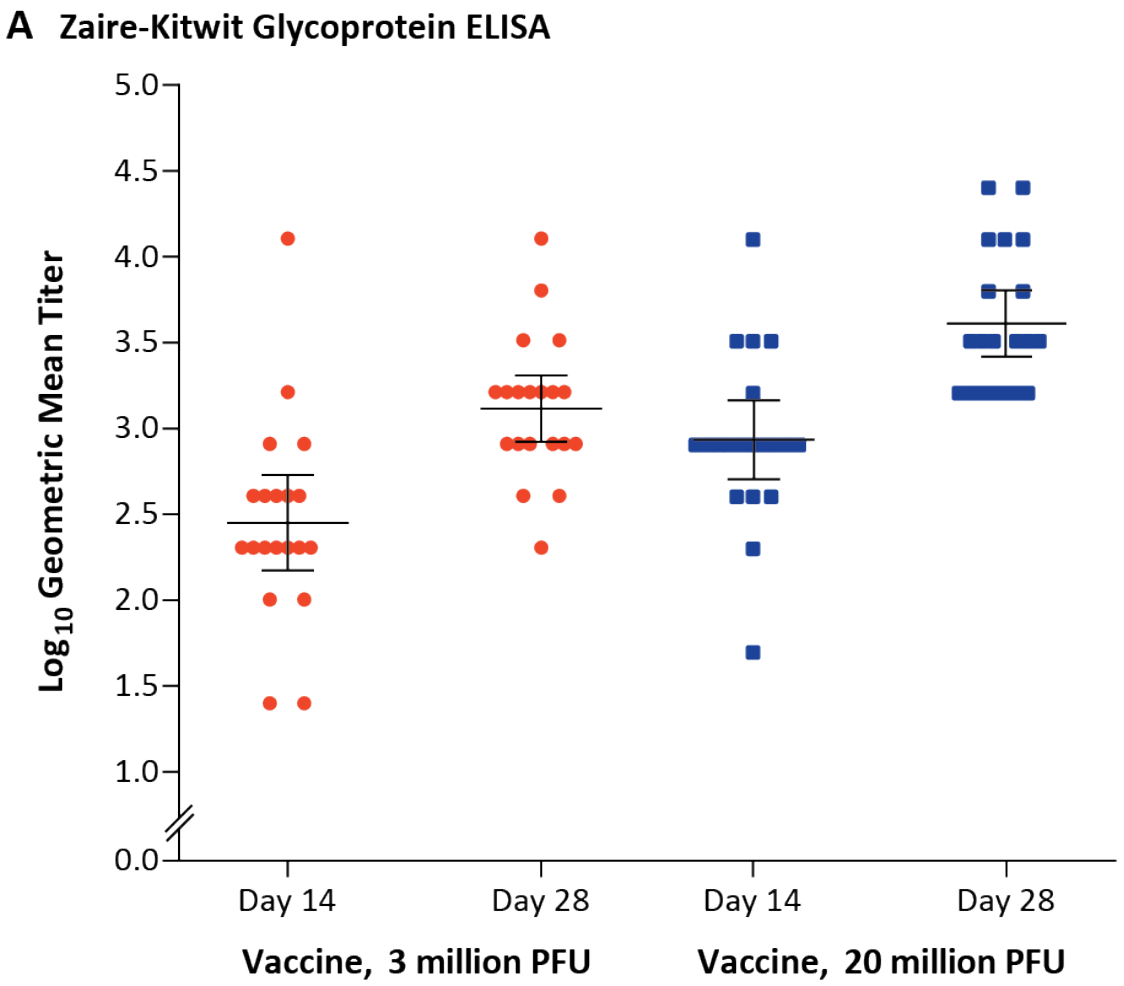


Figure from Regules, et al. NEJM (2015).
PFU=plaque forming unit.

Phase II/III Efficacy/Effectiveness Studies Ongoing

- NIH PREVAIL study in Liberia
  - Randomized placebo controlled trial
  - Phase II sub-study complete (N~500 V920 recipients)
  - Phase III portion of study (N~9000) on hold
- CDC STRIVE study in Sierra Leone
  - Immediate versus delayed vaccination in front line workers
  - N~6,000
- WHO study in Guinea
  - Immediate versus delayed ring vaccination
  - N~10,000
  - Also conducting safety study in front-line workers (N~1500-2500)

Bridging Non-human Primate (NHP) Data to Humans

Requirements

- Correlate-of-protection with protective threshold from NHP studies
  - Current efforts focused on IgG ELISA and/or neutralizing antibody
- Use of IgG ELISA assay requires translation of NHP threshold to human immunogenicity level
  - Options including use of common calibrating standard or common assay under consideration with collaborators
- Prospective test of human responses against the threshold
  - Samples retained from Phase II/III to be tested in validated clinical assay(s)
  - Hypothesis framed around acceptable percentage exceeding threshold

V920 Is a Promising Candidate Ebola Vaccine

- V920 vaccination protects NHPs against challenge
  - Further evaluation at lower vaccine doses to establish a threshold for protection
  - Further immunological characterization needed to bridge NHP threshold to humans
- V920 vaccine generates a rapid and robust antibody response in humans
- Phase II/III trials are ongoing
  - Samples from Phase II/III studies will be available to enable a prospective test of human immunity against a threshold